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43rd Annual Meeting

Oct. 19-21, 1961

The Tropicana
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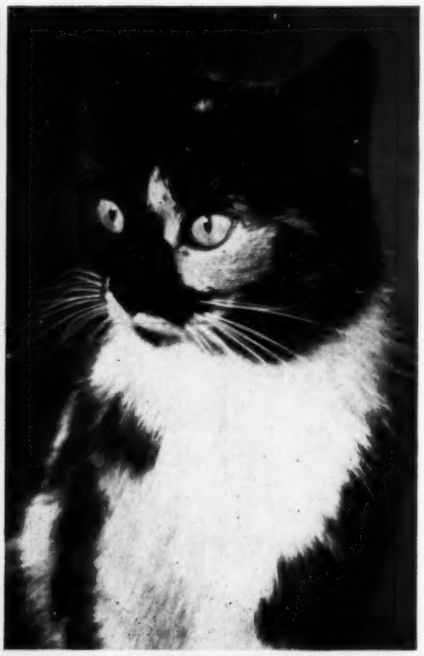

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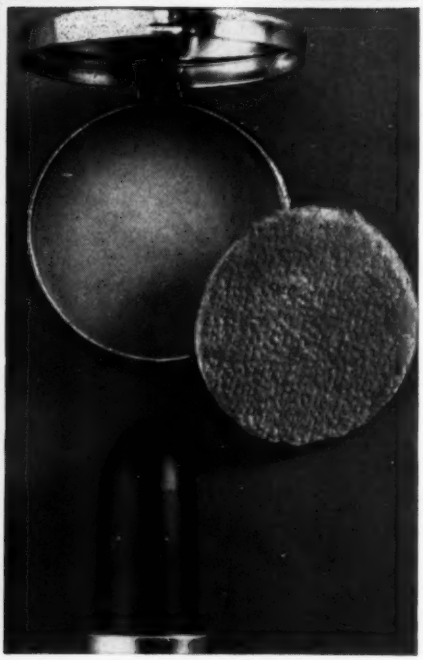

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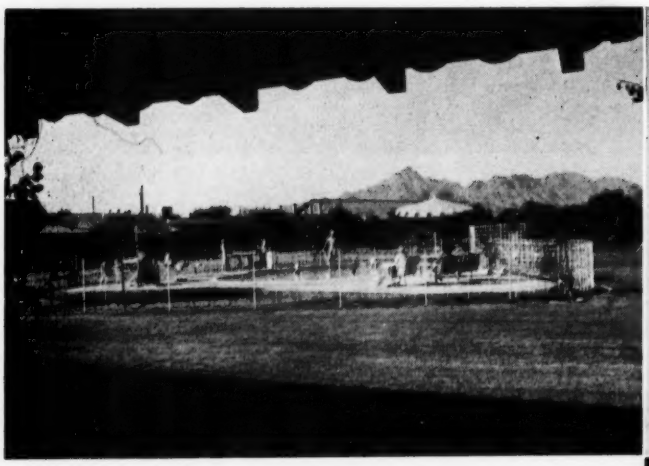

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Camelback Hospital

Santa Fe Seminar

Early Carcinoma of the Uterine Cervix

Program Chairman: Harry D. Ellis, M.D.
Case Presentation: Willis W. Pickel, M.D.
Discussion: Thomas R. Simon, M.D.

St. Vincent Hospital, *Santa Fe*

Case Presentation: Willis W. Pickel, M.D.

Case #1. The first case for discussion this evening is that of a 36 year old white woman in good health and without symptoms, who was given a routine periodic examination in 1956, and the cytologic smears taken from her cervix at that time revealed suspicious cells (Papanicolaou Class IV). Biopsy material taken from her cervix a short time later revealed an in situ carcinoma. Following this a total hysterectomy was done. Pathologic examination of the cervix revealed residual areas of in situ carcinoma and a single area of possible superficial invasion. No further treatment was undertaken. She is living and well four years and three months later.

Harry D. Ellis, M.D.

This first slide (Figure 1) shows a cluster of highly suspicious cells. I think everyone will agree that these should be classified as either Class IV or perhaps Class V.

The second slide from this case (Figure 2) shows a low power view of the cervical epithelium and towards the center you will notice an area in which the line between the epithelium and its supporting stroma becomes quite fuzzy. We did not feel this was clear cut evidence for microinvasion but did note that some people might consider it so.

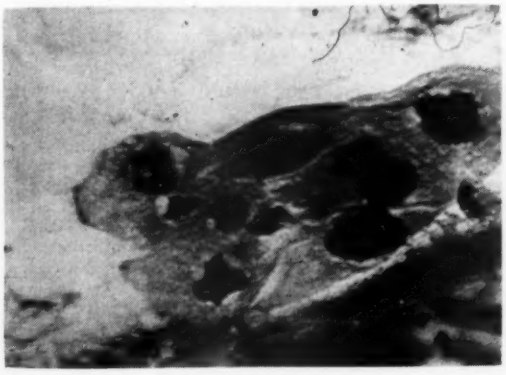

Figure 1

Case #1. Cytologic smear from cervix.

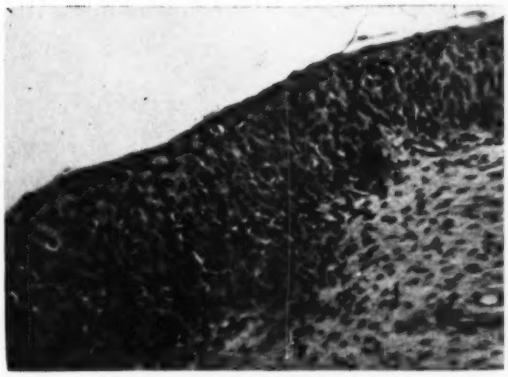

Figure 2

Case #1. Biopsy of cervix.

The next slide (Figure 3) is a higher magnification taken to show the rather marked variations in size, shape and staining of the cervical epithelial cells. The changes are present throughout the thicknesses of the epithelium and we felt that this did indeed represent surface or in situ carcinoma.

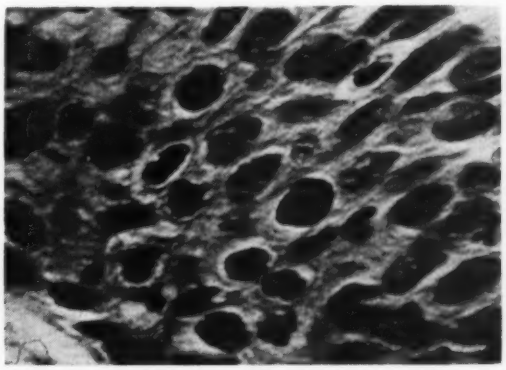

Figure 3

Case #1. Biopsy of cervix. (Higher magnification.)

Program supported by a grant-in-aid from Merck, Sharp and Dohme post-graduate program.

At this time I would like to introduce our guest speaker, Dr. Thomas R. Simon. Dr. Simon is Associate Professor of Pathology at Creighton University School of Medicine and is chief pathologist at the Creighton Memorial St. Joseph's Hospital. Dr. Simon is also the chairman of the Cytology Council of the American Society of Clinical Pathologists.

We are very fortunate in having a person with this background to conduct our seminar this evening. Dr. Simon.

Discussion: Thomas R. Simon, M.D.

This case illustrates the true value of routine cervical cytology. For two reasons carcinoma in situ is usually not visible to the naked eye. First, since it is only a few cell layers in thickness and since none of these is usually keratinized, the lesion tends to be transparent or translucent.

Secondly, the majority of these lesions, perhaps nine of ten, are located on the endocervical side of the squamocolumnar junction. In a series of 78 carcinomas in situ which we studied at one time 28, or 36 per cent, occurred in cervices which were considered entirely normal by the gynecologist, 45 showed gross erosion, ectropion, or evidence of inflammation, and just 5, or 6 per cent, showed gross leukoplakic areas which corresponded to the areas of in situ carcinoma.

The second point that this case brings up is the interpretation and importance of superficial infiltration. I think everyone is agreed that glandular extension is not evidence of invasion. Dr. Ellis and I agree that the term micro-invasive carcinoma should be reserved for those cases in which there are finger like extensions through the basement membrane which are not confluent and are not infiltrating lymphatic vessels. I would agree in reporting this case as "in situ carcinoma with some suspicion of microinvasion."

It is theoretically true that once tumor breaks through the basement membrane it has access to lymphatic vessels and, therefore, might well metastasize; so that it has often been said that the difference between early carcinoma and late carcinoma of the cervix is the barely demonstrable basement membrane. However, accumulated evidence suggest that this is not the case. Almost never has there been observed lymph node metastases from micro-invasive carcinoma.

Fidler and Boyes[1] report a series of 26 cases of micro-invasive carcinoma in none of which was there recurrence or metastasis. They suggest that the micro-invasive period is a relatively long one in which the host is exerting resistance to the growth of tumor, evidence of which they suggest can be seen histologically in one-half their cases. Therefore, our clinicians, like many others feel that sufficient treatment for in situ carcinoma with micro-invasion is hysterectomy.

Dr. Pickel

Case #2. The second case is that of a 47 year old woman whose pelvic examination revealed a small area which bled easily in an otherwise normal appearing cervix. Cytologic smears revealed suspicious cells (Papanicolaou Class IV) and subsequent biopsy of the cervix demonstrated both in situ and infiltrating carcinoma. Radiation therapy was given.

Dr. Ellis

The first slide in this case shows a cluster of highly suspicious cells (Figure 4). The second

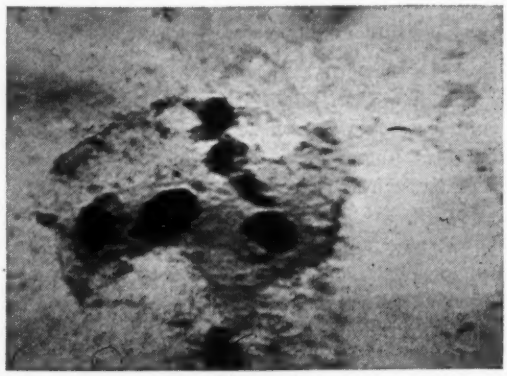

Figure 4
Case #2. Cytologic smear from cervix.

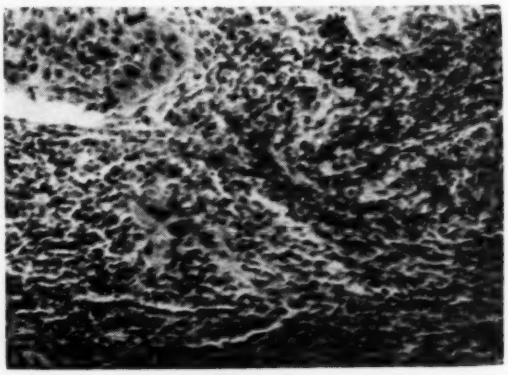

Figure 5
Case #2. Biopsy of cervix.

slide in this case simply shows an area of infiltrating carcinoma. There is a cluster of neoplastic cells in the upper left and in the middle of the picture which are somewhat obscured by a heavy surrounding inflammatory infiltrate (Figure 5).

Discussion: Dr. Simon

Under these conditions this case might also be considered a cytologic triumph although I suppose an area which bled easily would have been biopsied in the absence of cytologic studies. I mentioned in the previous case that carcinoma in situ is usually not visible to the naked eye, and I am sorry to have to report that in our hands the same may be true even of invasive carcinoma.

Among 25 invasive carcinomas which we have seen in the last three years, three occurred in cervices that were described by the clinicians as grossly normal, two of these were treated surgically and in one we were able to find no gross lesion in the laboratory although microscopic examination proved that the tumor extended to a depth of approximately one cm.

We feel that it is possible in almost every instance to predict the presence of invasion from the cytologic smears, and we modify the Papanicolaou classification so that in our terminology class IV means "suggesting in situ carcinoma," class V means "suggesting invasive carcinoma." Since we have adopted this practice I am aware of only one invasive carcinoma in which we did not suggest the likelihood of invasion cytologically.

On the other hand, among our cases which eventually proved to be in situ carcinoma, we had suggested the possibility of invasion falsely in approximately 30 per cent. Since in following our cases we rely heavily on punch biopsies, with which it is obviously not possible to rule out invasion, we feel that it is important to use this added guard against the possibility of invasion.

Even in the cases which have had cone biopsies we have used the cytologic suggestion of invasion to indicate continued study when only in situ carcinoma had been demonstrated, and in four such instances were eventually able to demonstrate invasion in additional material or in further study of the material available.

The criteria for invasion from a cytology smear are certainly not specific. They are: 1) presence of necrosis of epithelial cells and broken down red blood cells, 2) presence of bizzare forms of tumor cells, 3) presence of macronucleoli in tumor cells, and 4) presence of large numbers of inflammatory cells and abnormal bacterial flora.

There is some difference of opinion concerning the value of cytology in the presence of gross lesions. It is our feeling that gross lesions should be evaluated both by biopsy and cytologic smears. In addition cytologic diagnosis of invasive carcinoma is often somewhat more difficult than that of preinvasive carcinoma.

Dr. Pickel

Cases #3 and 4. The next two cases will be presented together. The first of the next two cases is that of a 43 year old woman in whom cytologic cervical smears revealed suspicious cells (Ayer's Class II B). These smears were taken during a routine examination. Biopsy of the cervix revealed chronic inflammation and epithelial dysplasia. The patient was followed with periodic cytologic smears and they were essentially normal for a period of one year. The smears them became highly suspicious (Ayer's Class III C).

On the basis of the smear report a total hysterectomy was done. Pathologic examination of the specimen removed revealed no areas of in situ or infiltrating carcinoma but there were areas of severe dysplasia and chronic inflammation of the cervix.

The second of these two cases is that of a 42 year old woman in whom routine cystologic smears revealed suspicious cells (Papanicolaou Class IV). Cervical biopsy revealed severe dysplasia and chronic inflammation. Endocervical and endometrial currettings were negative. Follow-up smears three months later revealed an absence of suspicious cells (Papanicolaou Class II).

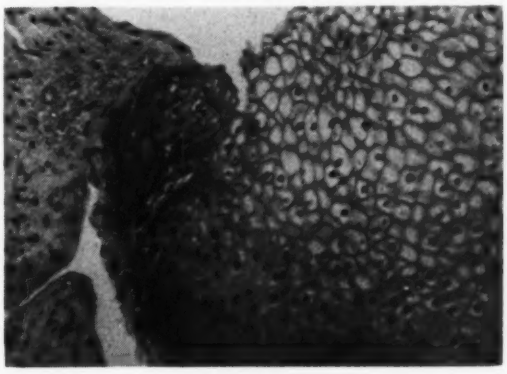

Figure 6
Case #3. Biopsy of cervix.

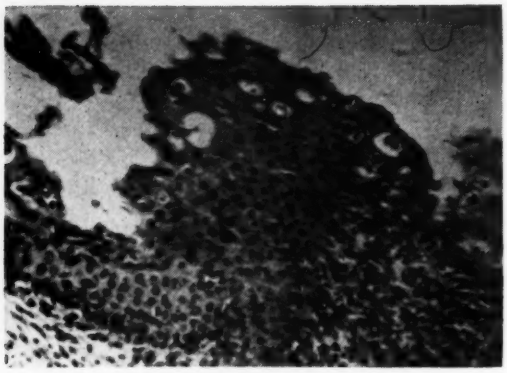

Figure 7
Case #3. Section of cervix from hysterectomy specimen.

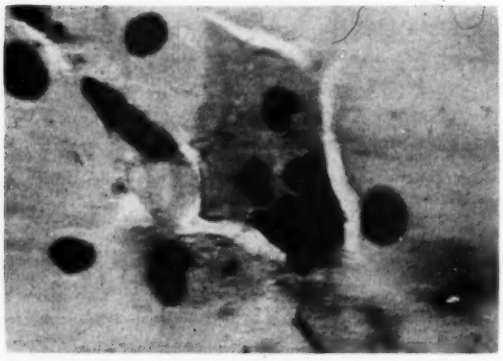

Figure 8
Case #4. Cytologic smear from cervix.

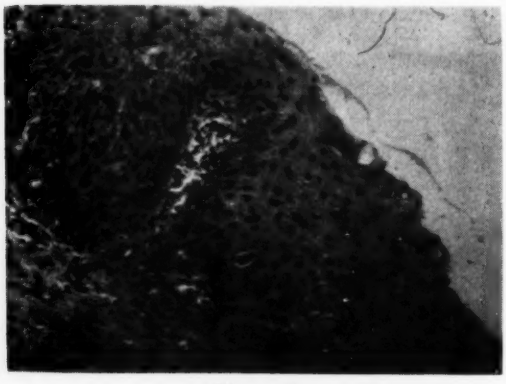

Figure 9
Case #4. Biopsy of cervix.

Dr. Ellis

I do not have a picture of the cells in the smears of the first of these two cases. This slide (Figure 6) is a picture of the original biopsy and it shows an area of mild dysplasia of the cervical epithelium. The next slide (Figure 7) is a photograph of the cervical epithelium from the cervix after removal by hysterectomy. Here you see a moderate degree of pleomorphism of the epithelial cells, a fairly heavy subepithelial inflammatory infiltrate, and small clusters of polys wandering through the epithelium. We did not feel this was in situ carcinoma but rather inflammation and dysplasia.

The next slide is from case No. 4 (Figure 8) and is a picture of a few rather suspicious cells in the cytologic smear. The next slide (Figure 9) shows the epithelium as seen in the biopsy material. There is a moderate degree of pleomorphism here but we did not feel that the changes were those of in situ carcinoma but representative of a degree of epithelial dysplasia.

Discussion: Dr. Simon

The problem of dysplasia is one that has arisen since the advent of the more or less routine use of cytologic examination. By dysplasia we mean alterations in adult cells manifested by variations in size, shape and orientation, different by definition from anaplasia in that the changes are actually or potentially reversible.

Under the microscope the dysplasias in contrast to the in situ carcinomas are a heterogenous group ranging from changes which vary from normal only slightly, up to changes which are practically indistinguishable from in situ carcinoma. Historically, dysplasia has been seen preceding and in association with carcinoma, in situ and invasive. With the exception of those dysplasias of the faintest degree of abnormality we have not found any group which consistently regresses, persists or advances.

Dysplasia has a tendency to appear on the portio vaginalis rather than in the canal; therefore, it tends to be detected in the cervical scraping rather than in the endocervical aspiration. Many cases show gross leukoplakia. In our hands, four point punch biopsy has cured fully one-third of the lesions, and we have no doubt that conization or cautery will cure the vast majority.

These cases point up the importance of correlating cytologic findings with histologic findings. I feel that one can hardly do consistently good cervical cytology or histology unless he has access to both smears and biopsies. Occasionally, we

diagnose smears as in situ carcinoma and find on biopsy only dysplasia.

Then review of the smears is imperative to see if they are explained by the biopsy or if they truly suggest that there is a lesion worse than the biopsy has revealed. One should not be satisfied with a diagnosis of dysplasia in the face of smears showing definite in situ carcinoma, keeping in mind that the two commonly coexist.

Dr. Pickel

Case #5. The 5th case is that of a 51 year old woman who had normal cervical smears in 1957, 1958 and in April, 1960 (Papanicolaou Class I). Physical examination in March, 1961, revealed the presence of an indurated purplish tumor mass surrounding the cervix and fornix, leaving the cervical os anatomically intact. The uterus was fixed and immobilized. Cytologic smears at this time revealed malignant cells (Papanicolaou Class V) and biopsy revealed an anaplastic infiltrating carcinoma.

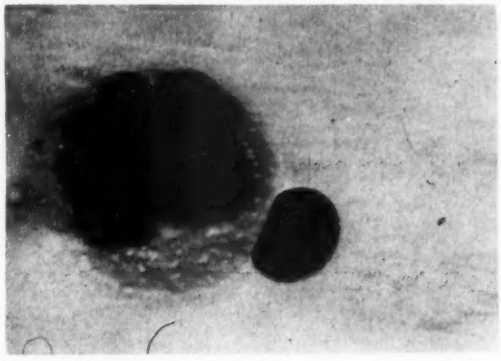

Figure 10
Case #5. Cytologic smear from cervix.

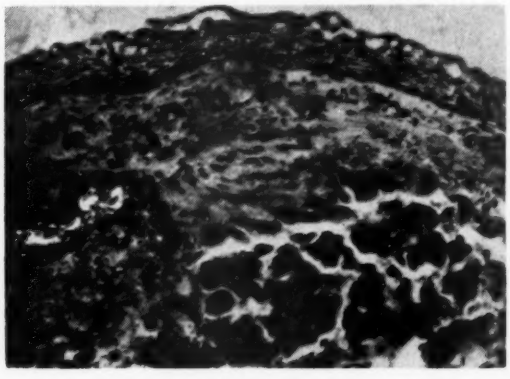

Figure 11.
Case #5. Biopsy of cervix.

Dr. Ellis

The first slide from this case (Figure 10) shows a large neoplastic cell as seen in the cytologic smear and the second slide, (Figure 11) shows a mass of highly anaplastic tumor cells lying in this picture, a short distance beneath a covering rim of epithelium. In other areas this tumor did ulcerate through the surface.

Discussion: Dr. Simon

This is an unusual and disturbing case, for it is obvious that periodic cytologic examination failed to protect this unfortunate patient from developing advanced pelvic carcinoma. We feel that since 1) in almost every case cervical epidermoid carcinoma goes through an in situ phase lasting several years and 2) cytologic study approaches 100 per cent accuracy in revealing the carcinoma during the in situ phase, employment of annual cytologic studies gives insurance against the development of advanced cervical epidermoid carcinoma.

There is some evidence that the same may be true for the relatively uncommon primary epidermoid carcinoma of vagina.

On review of the smears and biopsy in this case I agree that this is anaplastic carcinoma; however, I feel that there is a likely possibility that it is anaplastic adenocarcinoma and that it is metastatic to the site of the biopsy.

Dr. Pickel

Case #6. Case No. 6 is that of a 39 year old woman who reported to her physician for examination because of recent spotting. Examination of the cervix revealed a bleeding lesion of the cervical os. Cytologic smears were negative (Papanicolaou Class II). The biopsy specimen revealed the presence of an infiltrating squamous carcinoma. Radiation therapy was instituted.

Discussion: Dr. Simon

Well, I have run out of loop holes. The best thing I can say about this case is that there are not many like it. I looked at the smears before the meeting and would certainly agree that they are negative. It is not rare, as I mentioned earlier, that one has difficulty in finding suspicious cells in invasive carcinoma.

I don't recall our exact rate on this but I believe we have found malignant cells in about 85 per

cent of invasive carcinomas. However, in the remaining 15 per cent we have considered the smears suspicious because of the presence of necrosis, broken down blood, abnormal bacterial flora, etc. I don't know of another case that we have had that proved to be invasive carcinoma that had entirely negative smears.

Although it doesn't apply in this case, we might mention the reliability of different ways of taking smears. Originally we all examined vaginal smears only. It is our feeling that even in the best of hands, vaginal smears cannot find early carcinoma in more than 85 per cent of cases. On the other hand, we have found direct cervical smears to be positive or suspicious in about 97 per cent of cases of in situ carcinoma[2].

We advise the routine use of three smears, the cervical scraping, the vaginal aspiration, and the endocervical aspiration. The vaginal aspiration is superior in the detection of endometrial carcinoma and essential for hormonal evaluation. The endocervical aspiration is occasionally essential in the detection of in situ carcinoma arising high in the canal.

Dr. Pickel

Case #7. Our last case is that of a 32 year old woman in whom smears from the cervix were interpreted as Class IV, suspicious for in situ carcinoma, and a four point punch biopsy at that time showed carcinoma in situ in the 9:00 o'clock punch only. She was advised to come to the hospital for further treatment but did not return until three years later at which time she was seven months pregnant.

Cervical smears were again interpreted as Class V, suggesting carcinoma in situ. A cone biopsy sectioned in semi-serial fashion, showed extensive carcinoma in situ, not, however, extending beyond any of the margins of the excised specimen. At term a healthy child was delivered through normal channels. Subsequent cervical smears were negative. A hysterectomy was performed six weeks later and pathologic examination failed to reveal any residual tumor.

Discussion: Dr. Simon

In this case the cervix was originally considered grossly suspicious enough for biopsy, and smears taken at that time were suspicious for carcinoma.

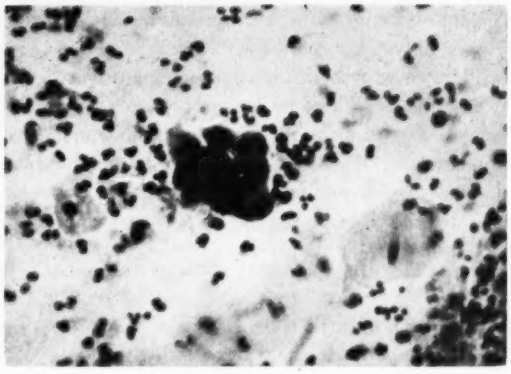

Figure 12
Case #7. Cytologic smear from cervix.

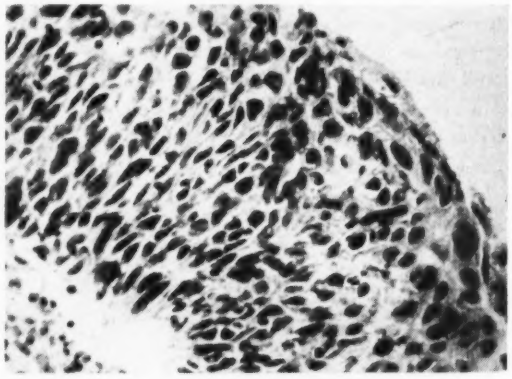

Figure 13
Case #7. Biopsy of cervix.

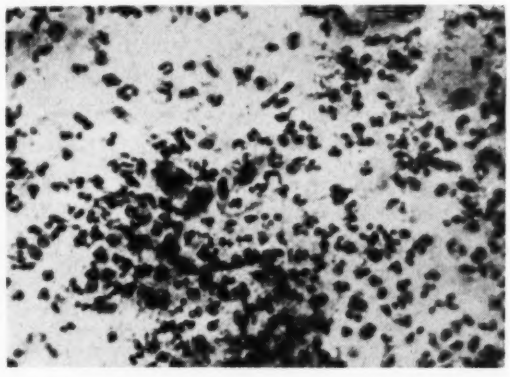

Figure 14
Case #7. Cytologic smear of cervix.

This slide (Figure 12) shows cells which are suspicious for in situ carcinoma. The next slide (Figure 13) shows an area of in situ carcinoma in the punch specimen.

We advised this woman to come to the hospital

to have a cone but she did not come back for over three years, at which time she was seven months pregnant. Again there were suspicious cells in her cytologic smear (Figure 14). The cone (Figure 15) showed extensive areas of carcinoma in situ.

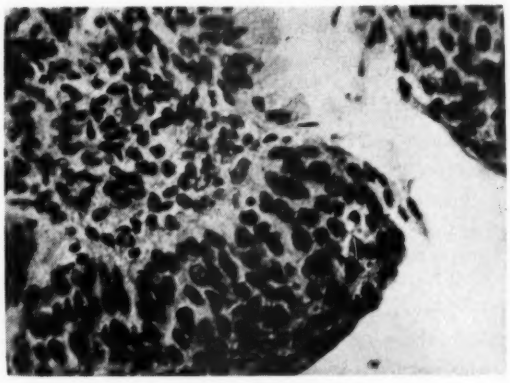

Figure 15
Case #7. Biopsy of cervix.

First, this case shows that carcinoma in situ may stay about the same for a considerable period of time. There have been very few cases closely followed in their entire course from normal, through in situ carcinoma, to invasive carcinoma. So that what information we have about the duration of the in situ phase is mostly from retrospective studies and from the difference in mean age between in situ and invasive carcinoma at the time of diagnosis.

From these it seems that he average duration of the in situ phase is eight to ten years. The few prospective studies I know of confirm this impression and further indicate that this phase is almost never less than one year in duration.

The second problem here is that of in situ carcinoma in pregnancy. Although it has been suggested that there is a reversible atypia (dysplasia), peculiar to pregnancy, which is indistinguishable histologically from in situ carcinoma, we and, I believe, most others feel that dysplasia, though certainly more common in pregnancy, is like dysplasia in the non-pregnant, and in situ carcinoma is in situ carcinoma in or out of pregnancy.

We feel that both cytologic studies and biopsies are liable to be less reliable during pregnancy. In our institution conization of the pregnant cervix has often been complicated by rather severe bleeding, but in no instance has it been implicated as interfering with the pregnancy.

The question arises as to what to do if the cone does not completely remove the lesion. Our choice has been to allow normal delivery, repeat the smears in four to six weeks, and if they are positive, proceed with hysterectomy. We have had one such case who had positive cytology at six weeks post-partum and micro-invasive carcinoma demonstrated in the hysterectomy specimen. She is well with no clinical disease after two years.

Discussion

Dr. Ellis

Dr. Milton Floersheim of Raton, New Mexico has a problem regarding treatment of a case of in situ carcinoma. His patient has a rather extensive in situ carcinoma and Dr. Floersheim has received suggestions for therapy which have ranged from x-ray therapy to simple hysterectomy to a radical Wertheim type of hysterectomy.

Dr. Simon

There is no agreement on the treatment of choice for in situ carcinoma of the cervix. In my opinion two of the methods you mention can be ruled out. (1) Although I would assume that x-ray therapy would effectively destroy this lesion, I am not aware of any organized proof of the efficiency of this method. In addition, there is the potential carcinogenic effect of radiation therapy in a group who may be expected to have long survival. Koss, Melamid, and Daniel[3] have recently reported nine cases of in situ carcinoma of cervix and vagina following radiotherapy for cervical cancer. (2) Radical Wertheim type of hysterectomy seems to be much more than is indicated since in theory in situ carcinoma should not metastasize and in practice I am aware of only one case[4] in which there was a metastasis from carcinoma of the cervix when careful study of the cervix failed to reveal invasion.

The most widely employed method of treatment of carcinoma in situ of the cervix is simple hysterectomy with an adequate vaginal cuff. However, under certain conditions we have relied upon conization as adequate therapy. These conditions include: (1) no tumor extension to

the cut margins of a completely studied conization specimen, (2) subsequent negative cytologic studies, (3) desire of patient to retain the uterus, usually because of the desire to have more children. To date we have had no case in which residual carcinoma was demonstrated after our study of the cone specimen had indicated that removal of the lesion had been complete.

Dr. Richard Angle

I have a 33 year old patient in whom the cytologic smear was reported as Class V. Cone biopsy is reported as completely negative. How would I handle this case?

Dr. Simon

I think that the first thing to do would be to review the cytology. I cannot visualize anything totally negative that would give rise to a Class V smear. I remember a case in which we had seven positive smears and five negative cervical biopsies, and finally examination revealed a small area of gross carcinoma of the vaginal wall.

I presume it is easy to miss a small carcinoma of the vagina, especially when the efforts are directed towards finding a lesion in the cervix. More likely for this case, however, would be that the lesion is high in the endocervical canal and was perhaps not included in the cone biopsy specimen. Certainly the smear should be repeated and a continued search be made for the source of the cells in the smears assuming that they remain positive.

Last year we saw an elderly patient in whom the smears were positive and the cone was negative. The uterus was removed and the report from the hysterectomy specimen was also negative. However, by re-examining the specimen very carefully, we were able to demonstrate an area of carcinoma in situ high in the endocervical canal. I think that this is somewhat more likely in the older age group in whom carcinoma tends to arise high in the endocervical canal.

Dr. Marcus J. Smith

Would you comment on the use of cytologic smears for follow-up of cases of cervical carcinoma after treatment by radiation?

Dr. Simon

Radiation produces profound changes in both squamous and endocervical cells and these changes may persist for long periods of time. To me, the cytologic changes in benign glandular cells are occasionally indistinguishable from those of adenocarcinoma.

Benign squamous cells show cellular and nuclear enlargement and smudging of nuclei which usually allow them to be distinguished from residual or recurrent carcinoma, in which the cells show sharp nuclear detail. In light of the previously mentioned study by Koss, careful cytologic follow-up of cases treated with radiation seems especially indicated.

My experience with cytologic prediction of radiation response is too limited to allow for comment on this aspect.

Dr. Ellis

Thank you very much Dr. Simon. I would like to take this opportunity to express my appreciation and the appreciation of the medical staff to you for your very fine discussions tonight. Our next seminar will be "Carcinoma of the Thyroid."

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American Fracture Association to Meet in Washington

The 22nd annual meeting of the American Fracture Association will be held in Washington, D. C., September 16 through September 23, 1961, with a postgraduate course at the Georgetown University Medical Center.

Participating in a panel discussion of "Fractures of the Distal End of the Radius" will be Dr. W. Compere Basom, El Paso; Dr. Russell Harris, Oklahoma City; Dr. William Johnson, Galesburg, Ill.; and Dr. Benjamin S. Meyer, Birmingham, Ala. Presiding over the panel will be Dr. Guillermo de Velasco Polo, well known orthopaedic sur- Dr. Robert Elliott of Houston, will participate in a geon from Mexico City. Another Southwesterner, panel discussion on "Supracondylar Fractures of the Femur."

Viruses and The Central Nervous System*

M. NATHAN KLEBAN, M.D., *El Paso*

Viruses are agents responsible for the greatest amount of minor illness, infectious disease, time lost from school or work, and for seeking the services of physicians. To have "a virus" is almost synonymous with being sick. We may say that we have a cold; the flu, plain, Asian, or intestinal; a bug; the crud; the trots; and other terms, hackneyed or fresh. A virus infection is probably what we are describing. The virus is the biological minute particle of the mid-20th century.

Intense spreading interest in the virus was made possible by the discovery of antibiotics, which eliminate bacterial contaminating interference in their study, and by development of tissue culture techniques.

The established relationship of viruses to tumors in experimental animals and the possible connection with human cancers is engaging the attention of a large segment of workers in the field of cancer research.

Finally, viruses stand in the shadowy area between the living and the non-living. The answer to the fascinating question of what differentiates life from non-life may well lie in the structure and behavior of virus particles.

Luria, in 1953, defined viruses with these restrictions: viruses are entities, sub-microscopic in size, which reproduce only inside specific living cells, and into which they can be introduced from without.

This is his definition in 1958: that viruses be considered as "genetically specific cell constituents, containing coded DNA or RNA (deoxyribose nucleic acid and ribose nucleic acid) which can, as one of their genetic functions, determine their own incorporation into specific vehicles for transmission to other cells." DNA or RNA with protein overcoat are from 10-15 mμ up to 200-250 mμ in diameter. Red blood cells are about 7500 and bacteria about 750 mμ.

In 1891 Nordmeyer introduced a compressed infusorial earth material as a filter, named after the owner Berkefeld of the Kieselguhr mine in Hannover, which separates most bacteria from most viruses and from whence derives the term "filterable viruses". A Russian, Ivanovski, is credited with discovery of tobacco mosaic virus disease in 1892, which he thought was due to bacteria. Most viral work for many years was on this plant virus and the bacterial virus, phage.

In a discussion of the incidence of virus disease in man, whether of the central nervous system or not, there are several general things to be con-

*Presented at District One, Texas Medical Association, meeting at Pecos, Texas, Feb. 5, 1960.

sidered. Virus may be recovered from throat washings or stools in the absence of clinical illness. Studies have demonstrated a high rate of infection in families of polio patients. But manifestations of illness may range from none through symptoms of gastro-enteritis, upper respiratory infection or aseptic meningitis to paralytic polio.

Epidemic

During an epidemic of St. Louis encephalitis in Cameron County, Texas,[1] in 1957 the ratio of inapparent to apparent cases was 64:1. Influenza may cause illness ranging from a mild upper respiratory infection to a fatal pneumonia. On the other hand, what we term as influenza-like illness may be caused by some 10 different known viruses.

There is increasing evidence of overlapping of clinical manifestations by different viruses; without laboratory studies one may not be able to distinguish betwen a paralytic illness caused by a polio, Coxsackie or ECHO virus. One can't tell the players without a score card. Published estimates of the incidence of influenza in Texas in the winter of 1959-60 have been unreliable in the absence of culture and hemagglutination-inhibition studies.

The reported ratio of paralytic to non-paralytic polio is rising. There were 1180 paralytic to 1156 non-paralytic cases of polio reported in Texas for the first 48 weeks of 1954. Comparable figures were 350 + 354 in 1957, 380 + 180 in 1958 and 319 + 199 in 1959. ECHO and Coxsackie viruses were found frequently in the reported non-paralytic cases but rarely in reported paralytic cases.

During 1958 the Communicable Disease Division of the Texas State[2] Department of Health studied 530 cases of suspected polio. Polio virus was cultured from stools or nasopharyngeal specimens in 131, Coxsackie viruses in 61, and ECHO in 22. There were 21 confirmed arthropod-borne encephalitis cases in Texas for an unknown part of 1959.

In 1953 in a study of 854 cases of aseptic or nonbacterial meningitis the etiology was unknown in 75 per cent; mumps 12 per cent; lymphocytic choriomeningitis nine per cent; leptospirosis three per cent; and herpes simplex one per cent.[3] In another study in 1955-56 it was found that Coxsackie, ECHO and polio viruses each accounted for approximately 15 per cent. During 1955-56 viral studies were made of 1407 patients with clinical manifestations of infectious disease of the central nervous system.[4]

On the basis of isolation of virus or serologic evidence of infection of 120 cases of aseptic meningitis four per cent were due to polio virus, 28 per cent to Coxsackie, nine per cent ECHO, two per cent herpes simplex. All of the above viruses were implicated in encephalitis and in paralytic polio.

On the basis of electroencephalographic tracings of 1298 children at the Municipal Hospital for Contagious Diseases in Chicago the common contagious diseases of childhood involve the cerebral cortex more frequently than is clinically recognized.[5] These patients had measles, mumps, chickenpox, scarlet fever and rubella. Seventy had symptoms of encephalitis and had abnormal EEG tracings. Of the remainder there were 470 abnormal tracings, about 30 per cent.

Etiological Diagnosis

The Division of Laboratories, Texas State Department of Public Health, Austin, under Dr. J. V. Irons (Sc.D.), can be of considerable assistance in establishing an etiological diagnosis of non-bacterial infections of the central nervous system. It is a good idea to obtain 5-10 c.c. of blood under aseptic conditions, to avoid bacterial contamination with possible resulting hemolysis, and to refrigerate the separated serum. This may then be sent in with a second specimen 2-4 weeks later for appropriate serological examination.

Complement fixation tests are done for suspected typhus, Rocky Mountain spotted fever, rickettsialpox and Q fever; lympho-granuloma venereum-psittacosis group; adenovirus group; mumps; St. Louis, Western and Eastern encephalomyelitis; lymphocytic choriomeningitis; polio types I, II and III; leptospirosis; toxoplasmosis. Tests are done only for diseases suspected.

Virus recovery and identification tests are available for suspected small pox, herpes, polio, ECHO, Coxsackie and others. Serological tests are not practical for Coxsackie and ECHO because of the large number of viruses comprising

these groups. Fresh unpreserved stools should be sent by air or overnight by express on ice.

Spinal fluid should be obtained for recovery of Coxsackie or ECHO viruses. Mere presence of these viruses in the intestinal tract does not incriminate them. Their presence in the spinal fluid does. Polio viruses are not generally recovered from spinal fluid. Rabies constitutes a special problem. Greater use could probably be made by pathologists of the State Health Department services in viral studies on tissues obtained for biopsy or at autopsy.

There are about 50 arthropod borne viruses transmitted by mosquitoes, ticks, sand flies. Western equine of Group A and St. Louis of Group B are endemic in our area.

Virus Isolated

Coxsackie, New York, was the home of two boys suffering from paralytic polio whose stools supplied a virus isolated by Dalldorf and Sickles. There are now 24 members of the Coxsackie family. These are divided into 19 Group A types or strains and five Group B. When inoculated into suckling mice Group A Coxsackie viruses produce paralysis because of degeneration of skeletal muscle. Group B infected mice exhibit tremors, spasticity and spastic paralysis.

Coxsackie is the causative agent of epidemic myalgia or pleurodynia or Bornholm's disease or devil's grip, which may produce excruciating muscular pains in any region. When it involves the diaphragm recognition is simple. Coxsackie also produces herpangina. There are characteristic grayish-white papules or vesicles surrounded by erythema which may go on to ulcerate and may be seen on the anterior faucial pillars, palate, uvula, tonsils or tongue. Coxsackie viruses have produced fatal myocarditis in the newborn within the first eight or nine days of life. Coxsackie has been implicated in adult myocarditis and pericarditis.[6]

ECHO—enteric cytopathogenic human orphan —virus started out in 1952 in search of a disease. There are now 24 antigenically distinct types and diseases have been found for them. Sanford and Sulkin propose the term enterovirus disease because of the overlapping spectrum of clinical disorders which the polio, Coxsackie and ECHO viruses may produce.[7] Horsfall and Rivers compare the enteroviruses in the following manner:[8]

Polio Viruses

1. Paralysis—complete to slight muscle weakness. 2. Aseptic meningitis. 3. Undifferentiated febrile illness, particularly during the summer.

Coxsackie, Group A

1. Herpangina. 2. Aseptic meningitis. 3. Undifferentiated febrile illness, particularly during summer. 4. Febrile illness with rash.

Coxsackie, Group B

1. Mild paralysis?—encephalitis. 2. Aseptic meningitis. 3. Undifferentiated febrile illness with pharyngitis. 4. Pleurodymia. 5. Myocarditis or encephalomyocarditis during neo-natal period and early childhood.

ECHO

1. Mild paralysis?—or encephalitis. 2. Aseptic meningitis. 3. Undifferentiated febrile illness. 4. Febrile illness with rash. 5. Summer diarrhea of infants and children.

A case of acute cerebellar ataxia in a five-year-old boy with recovery of ECHO virus from the spinal fluid has been reported recently.[9]

Wallgren set out these criteria for aseptic meningitis in 1925: (1) Acute onset with symptoms and signs of meningeal involvement; (2) cerebrospinal fluid changes of meningitis; (3) absence of bacteria; (4) relatively short benign course of illness; (5) absence of juxtameningeal or systemic disease of which meningitis might be a secondary manifestation; and, (6) absence from the community of epidemic disease of which meningitis is a feature.

The last is not valid today. Normal spinal fluid sugar and a count generally not over a thousand with the predominant cell usually the lymphocyte, although polys may be the majority early, may be added.

The Infectious Disease Service of University Hospital of the Ohio State School of Medicine during the last two years has routinely submitted stool and spinal fluid specimens to the Ohio State Department of Health on all patients with aseptic meningitis.[10] They recently reported 11 cases in which Coxsackie virus was isolated from six spinal fluids and ECHO in five. There was recovery of

virus in only five stools. They had previously reported 11 cases of aseptic meningitis due to leptospires.

As an example of the unexpected central nervous system effects of mumps, which is ordinarily considered an innocuous infection, unless it occurs in an adult male, there recently was reported two patients with sudden onset of coma.[11] In both instances the parotid glands were not enlarged, and the parents insisted both boys had had the mumps many years before. Mumps virus was recovered from the spinal fluid of both patients.

Worldwide Epidemics

Independent reviews recently appeared in the New England Journal of Medicine and The American Journal of Medicine advocating that a single or related group of causative agents was responsible for 22 curious, intriguing epidemics occurring worldwide from 1934 at Los Angeles County Hospital to 1958 at an Athens, Greece, hospital.[12]

Paresis was present in all outbreaks, but not in all individuals. Nurses and doctors have been most frequently involved. In addition to paresis other characteristics have been headache, pain of almost all parts of the body, prodromal sore throat, paresthesias, muscle cramp, depression, impaired mentation, vertigo, diplopia, photophobia, g-i symptoms, urinary retention, nuchal rigidity, low grade fever or none, and nystagmus. Muscle pains were often agonizing.

Paresis usually affected those parts most painful and tender. Paresthesias and hypesthesias usually occurred in limbs affected by paresis. Bizarre, shifting neurological findings frequently suggested hysteria. The acute phase lasted days to weeks; symptoms resolved slowly and were frequently punctuated by exacerbations. The most persistent and incapacitating symptoms were fatigability, malaise, headache, neck, back and extremity pain, paresis, depression, irritability, impairment of concentration, paresthesias, tremor and involuntary movements.

Debility was protracted. Average time lost from work in the Los Angeles outbreak was 3½ months; one-fourth lost over five months. Only 13 per cent of 39 followed at the end of six years after the Iceland outbreak considered themselves free of symptoms.

Sedimentation rate was rarely elevated. Pleocystosis and elevation of cerebrospinal fluid protein has been rare. Electroencephalograms were almost all normal. Most patients recovered completely in 1-2 months.

It is suggested that sporadic cases be diagnosed only when there are almost all the characteristic findings plus paresis or other objective evidence of neurological involvement. No etiological agent has yet been found. One author proposes that this disease entity, if such it is, be called Epidemic Neuromyasthenia. The other author proposes Benign Myalgic Encephalomyelitis.

Rabies

Rabies is a form of encephalitis caused by a virus which exists as a salivary gland infection in carnivorous animals, is usually transmitted to man by a dog, and is carried asymptomatically by bats. One person in 10,000 receiving the Semple rabbit brain Pasteur treatment develops a sensitization encephalomyelitis; one in 35,000 will die of bulbar paralysis. Use of egg embryo virus vaccine avoids this danger. Post-infectious encephalomyelitis following measles and chicken pox and post-vaccinial encephalomyelitis after vaccinia innoculation are believed to be sensitization reactions.

Psittacosis-lymphogranuloma venerum particles, which are more closely related to rickettsias than to viruses, may produce a meningo-encephalitis.

The virus of lymphocytic choriomeningitis is 40-60 mμ in size, is transmitted to man by mouse excretions, produces early grippe-like symptoms and only rarely results in paralysis or death. Diagnosis is made by isolation of the virus from cerebrospinal fluid, neutralization or complement-fixation tests.

Meningo-encephalitis may be the initial or sole manifestation of mumps infection.

The virus of encephalomycarditis shares with ECHO viruses the ability to hemagglutinate. A strain of this virus was isolated from the cerebrospinal fluid of a girl with Guillain-Barré type of polyneuritis. Heart involvement has been found only in animals. This virus is capable of causing paralysis, encephalitis and aseptic meningitis in humans.

Generalized salivary gland virus infection or cytomegalic inclusion disease virus produces intra-

cytoplasmic and intranuclear inclusion bodies. The disease is said to be generally fatal in young infants. Diagnosed disease in adults has been rare, although subclinical infection may be common.

There have been other cases of inclusion disease with cytoplasmic inclusion bodies, variable neurologic signs, mental deterioration and fatal termination in 2-6 months.

Infectious polyneuritis or Guillain-Barré disease, with protein-cell dissociation in the cerebrospinal fluid, remains of unknown etiology although thought to be due to a viral agent.

Hemorrhagic meningoencephalitis is reported to be a disease entity of viral etiology. Von Economo's encephalitis lethargica has not been reported in epidemic form since 1926. Reports of individual cases remain unverified, since no specific virus has been recovered.

Control and Therapy

Rickettsiae resemble gram negative bacteria, are able to metabolize independently in vitro, reproduce by binary fission only within living cells, and are inhibited by available drugs such as chloramphenicol and tetracyclines.

The largest of the viruses, the psittacosis-lymphogranuloma-trachoma group, stain with basic dyes, are visible with the ordinary microscope, filter with difficulty, are presumed to divide by binary fission, and produce disease treatable with sulfonamide derivatives and antibiotics.

No other human virus diseases are affected by available drugs. Primary atypical pneumonia is of possible but unproved viral etiology which may be an exception. Use of antibiotics in this illnesss has led to uncertain and contradictory conclusions.

Virus particles use the host cell energy systems for duplication of their ribose and deoxyribose nucleic acids and protein shells. In this parasitic relationship lies the probable explanation for failure of available drugs to influence viral infectious diseases.

Experimental anti-viral substances include acridines, pentamidine, stilbamidine; benzimidazoles which inhibit nucleic acid synthesis; K. pneumoniae poly-saccharide which inhibits mumps virus multiplication in the egg embryo; helenine, a nucleoprotein derived from penicillium funiculosum.

Interferon, a protein obtained from virus production in tissue culture, somewhat smaller than antibody, offers tantalizing promise of viral inhibitory activity without injury to the host cells. The properdin system is of experimental interest in the mechanism of resistance to virus infection.

Active immunization is of the greatest practical importance in control of virus disease. Attenuated live virus vaccine is used for protection against yellow fever and smallpox. In polio immunization there remains the problem of increasing the effectiveness of parenteral vaccine. A disturbing incidence of paralytic and fatal polio in individuals who had received three or four injections of the commercial Salk vaccine occurred in Boston in 1959. The issue of killed parenteral versus live attentuated oral vaccine has not yet been settled.

Polyvalent killed influenza vaccine is 75-80 per cent protective up to several months although for a much longer period if suspended in Freund's mineral oil adjuvant.

There is experimental work in measles immunization with both measles and distemper viruses. Mumps immunization must be repeated annually. The adenovirus vaccine will have little importance, because the incidence of apparent adenovirus infection is low. Rabies can be controlled by vaccination of animals.

Modification or prevention of measles and infectious hepatitis by passive immunization with gamma globulin is definite. Of equivocal value is the use of gamma globulin in prevention of rubella in the first trimester of pregnancy and of mumps in man. If used the dosage should be 20-30 c.c.

Deaths in children on steroids who have developed chicken pox have been reported. But steroids are being used in encephalomyelitis. The balance is between decrease of edema and inflammation and the function of adrenocortical hormones in stress and interference with localizing and immune processes.

Virus infection involves admission to the body; collission with, adsorption to and penetration of the host cell; disintegration and a dormant state of the virus particle or multiplication of virus material and fragmentation of the host cell. The

mechanism of host cell susceptibility or resistance is unknown. Interference and synergism between different viruses have been demonstrated.

Conclusion

Although people want magic bullets for virus infections none are as yet available. Placebo injections are as effective as penicillin and carry no risk of serious anaphylactic reactions or producing resistant staph super-infections. Placebo infections are 50 per cent effective in lowering the incidence of common cold infections. Needed is a simple wide-spectrum laboratory procedure for diagnosis of virus infections, particularly of the central nervous system. A combined viral vaccine, requiring boosters no more often than every 3-5 years if killed and given parenterally or safe from mutation and intereference if attenuated live and given orally, is the viral immunization objective. With protection against the 48 known types of ECHO and Coxsackie viruses the incidence of respiratory, intestinal, muscular and central nervous system infections would plummet.

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Coming Meetings

Postgraduate Course in Pediatrics, The University of Colorado School of Medicine, Stanley Hotel, Estes Park, Colorado, August 21-25, 1961.

El Paso Branch, University of Texas Postgraduate School of Medicine, El Paso County Medical Society's Turner Home, 1301 Montana Avenue, El Paso, Sept. 10, 1961.

American Heart Association, 26th annual meeting, Shamrock Hilton Hotel, Houston, Sept. 15-17, 1961.

American Fracture Association, 22nd annual meeting, Georgetown University Medical Center, Washington, D.C., Sept. 16-23, 1961.

Western Association of Railway Surgeons, Annual Meeting, Holiday Hotel, Reno, Nev., Sept. 28-30, 1961.

Arizona Academy of General Practice, Annual Scientific Session, Ramada Inn, Tucson, Oct. 12-14, 1961.

Southwest Obstetrical & Gynecological Society, Eleventh Annual Meeting, Konakai Club, San Diego, Oct. 15-17, 1961.

Southwestern Medical Association, 43rd Annual Meetings, Tropicanna Hotel, Las Vegas, Nev., Oct. 19-21, 1961.

MEETINGS

Western Association of Railway Surgeons To Meet September 28-30 in Reno

The annual convention of the Western Association of Railway Surgeon will be held at the Holiday Hotel in Reno, Nevada September 28, 29 and 30. The social activities during this meeting will include a trip to Virginia City on Thursday afternoon, September 28th, and a trip to Squaw Valley on Friday afternoon, September 29th. The annual banquet will be held at the Holiday Hotel Friday evening.

There will be an address by Mr. Francis B. Lewis, Manager of Safety and Courtesy, Union Pacific Railroad. In addition our program will include the following papers:

The Management of Cystic Disease of the Breast

Ruth Fleming, M.D., Reno, Surgeon, Western Pacific Railroad.

Hazards of Transfusions

Maurice E. Leonard, M.D., Associate Professor of Clinical Medicine at the Univerity of California and Senior Consulting Internist, Western Pacific Railroad.

Traumatic Rupture of the Diaphragm

Max Childress, M.D., Assistant Clinical Professor of Surgery at the University of California and Chief Counsulting Thoracic Surgeon, Western Pacific Railroad.

Evaluation of the Patient with Acute Myocardial Infarction

John M. Read, M.D., Elko, Nevada.

Experience with Peripherovascular Disease at Southern Pacific General Hospital

Bradford Simmons, M.D., San Rafael, Calif., and
Charles J. Monahan, M.D., San Francisco

Panel Discussion: Bronchogenic Carcinoma

1. Clinical Diagnosis
   H. Corwin Hinshaw, M.D., Clinical Professor of Medicine, Stanford University.

2. Bronchoscopic and Laboratory Diagnosis
   Horton C. Hinshaw, M.D., San Francisco.

3. Surgical Treatment
   Albert C. Daniels, M.D., Assistant Clinical Professor of Surgery, Stanford University.

There will also be a panel discussion on Cardiology with particular reference to the rehabilitation of cardiac cases. Participating in this will be Bernard Kaufman, Sr., M.D., Medical Superintendent, Southern Pacific General Hospital; John Read, M.D., Elko, Nevada; Emery R. Calovich, M.D., Kansas City, Missouri, Consultant Cardiologist, Union Pacific Railroad.

The annual William T. Cummins Memorial Lecture of the Western Association of Railway Surgeons will be given by Dr. Angelo Lapi, M.D., of Kansas City, Missouri. Dr. Lapi is Professorial Lecturer in Law Medicine at the Kansas City University School of Law. He is Assistant Professor of Clinical Pathology at the University of Kansas Medical Center, Pathologist at St. Mary's and St. Margaret's Hospitals in Kansas City and President of the Missouri Society of Pathologists. The exact title of his address has as yet not been determined but it will be concerned with the Medico-Legal aspects of Pathology in which Dr. Lapi has had vast experience.

Speakers Named for Southwestern Medical Association Meeting

The 43rd annual meeting of the Southwestern Medical Association will be held in the Tropicana Hotel, Las Vegas, Nevada, October 19-21, 1961.

Guest speakers for the meeting will be:

Orthopedics, Dr. Benjamin Fowler, Nashville.

Ophthalmology, Dr. Max Fine, Associate Clinical Professor of Ophthalmology, University of California Medical School.

Internal Medicine, Dr. William Parson, Charlottesville, Professor of Internal Medicine, University of Virginia School of Medicine.

Surgery, Dr. O. T. Claggett, Surgical Section, Mayo Clinic.

Obstetrics, Dr. Cary M. Dougherty, Clinical Associate Professor of Obstetrics and Gynecology, Louisiana State University School of Medicine.

Dermatology, Dr. Arthur Curtis, Professor of Dermatology, University of Michigan School of Medicine.

Registration fee will be $25, which will include two round table discussion luncheons at the Tropicana. It will be an open meeting, and all doctors are invited.

Dr. Sherwood Burr of Tucson is President of the Association. Other officers are Dr. Harold J. Beck, Albuquerque, President-Elect; Dr. David Russek, Chihuahua City, Vice President; and Dr. Merle D. Thomas, El Paso, Secretary-Treasurer.

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